

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO (if known, see 37 CFR 1.5)

09/673686

INTERNATIONAL APPLICATION NO.
PCT/RU98/00143INTERNATIONAL FILING DATE
MAY 18, 1998PRIORITY DATE CLAIMED
APRIL 20, 1998

TITLE OF INVENTION

METHOD FOR PRODUCING A SPECIFIC ANTISERUM AGAINST THE UNIVERSAL TUMOROUS
ANTIGEN AND METHOD FOR DIAGNOSING MALIGNANT TUMOURS USING SAID ANTISERUM

APPLICANT(S) FOR DO/EO/US

VALENTIN SERGEEVICH ERKHOV

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. This is an express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. is transmitted herewith (required only if not transmitted by the International Bureau)
 - b. has been transmitted by the International Bureau.
 - c. is not required, as the application was filed in the United States Receiving Office (RO/US).
6. A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a. are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. have been transmitted by the International Bureau.
 - c. have not been made; however, the time limit for making such amendments has **NOT** expired.
 - d. have not been made and will not be made.
8. A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. A **FIRST** preliminary amendment.
 A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. A substitute specification.
15. A change of power of attorney and/or address letter.
16. Other items or information:

Small Entity Declaration, Form 210
Copy of WO cover page

APPLICATION NO. (if known, see 37 CFR 1.5)

09/673686INTERNATIONAL APPLICATION NO
PCT/RU98/00143ATTORNEY'S DOCKET NO
ERKHOV-1 (PCT) The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO..... **\$860.00**
 International preliminary examination fee paid to USPTO (37 CFR 1.482)
 **\$710.00**

Neither international preliminary examination fee paid (37 CFR 1.82) nor
 international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **\$1000.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482)
 and all claims satisfied provisions of PCT Article 33(2)-(4)..... **\$100**

ENTER APPROPRIATE BASIC FEE AMOUNT =

CALCULATIONS

PTO USE ONLY

\$1,000.00

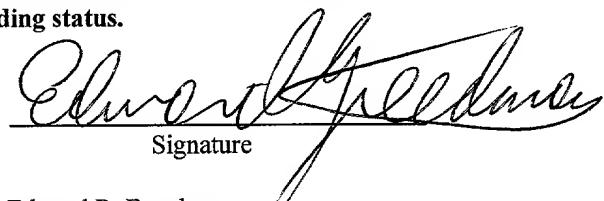
Surcharge of **\$130.00** for furnishing the oath or declaration later than **20** **30**
 months from the earliest claimed priority date (37 CFR 1.492(e)).

Claims	Number Filed	Number Extra	Rate	
Total Claims	4 - 20 =	- 0 -	X \$18.00	\$
Independent Claims	2 - 3 =	- 0 -	X \$80.00	\$
Multiple dependent claim(s) (if applicable)			+ \$270.00	\$
TOTAL OF ABOVE CALCULATIONS =				\$
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				\$ 500.00
SUBTOTAL =				\$ 500.00
Processing fee of \$130.00 for furnishing the English translation later than 20 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$
TOTAL NATIONAL FEE =				\$ 500.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				See cover sheet attached to assign \$ to be charged to Deposit Acct
TOTAL FEES ENCLOSED =				\$ 500.00
				Amount to be: refunded
				\$
				charged
				\$

- A check in the amount of \$500.00 to cover the above fees is enclosed.
- Please charge my Deposit Account No. 03-2468 in the amount of \$ to cover the above fees. A duplicate copy of this sheet is enclosed.
- The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-2468. A duplicate copy of this sheet is enclosed.

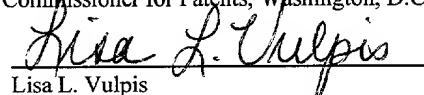
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
 COLLARD & ROE, P.C.
 1077 Northern Boulevard
 Roslyn, New York 11576-1696
 (516) 365-9802


 Signature
Edward R. Freedman
Reg. No. 26,048

Express Mail No. **EL 621 998 742 US**
 Date of Deposit October 19, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, on the date indicated above, and is addressed to the Ass't. Commissioner for Patents, Washington, D.C. 20231


 Lisa L. Vulpis

09/673686

422 Rec'd PCT/PTO 19 OCT 2000

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: VALENTIN SERGEEVICH ERKHOV-1 (PCT)

PCT No.: PCT/RU98/00143 FILED: MAY 18, 1998

TITLE: METHOD FOR PRODUCING A SPECIFIC ANTISERUM AGAINST THE UNIVERSAL TUMOROUS ANTIGEN AND METHOD FOR DIAGNOSING MALIGNANT TUMOURS USING SAID ANTISERUM

PRELIMINARY AMENDMENT

BOX PCT

Ass't. Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to the initial Office Action, please amend the above-identified application as follows:

IN THE ABSTRACT

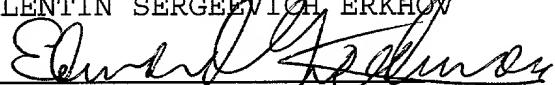
Please add the Abstract, attached hereto on a separate sheet, to the end of the application.

REMARKS

By this Preliminary Amendment, the Abstract has been added so as to avoid the surcharge associated therewith. Entry of this amendment is respectfully requested.

Respectfully submitted,
VALENTIN SERGEEVICH ERKHOV

COLLARD & ROE, P.C.
1077 Northern Boulevard
Roslyn, New York 11576
(516) 365-9802
ERF/llv

By: 
Allison C. Collard, Reg. No. 22,532
Edward R. Freedman, Reg. No. 25,048
Attorneys for Applicant

EXPRESS MAIL NO. EL 621 998 742 US

Date of Deposit: October 19, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, on the date indicated above, and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.


Lisa L. Vulpis

ABSTRACT OF THE DISCLOSURE

The present invention pertains to the field of medicine and may be used for producing a specific antiserum as well as for carrying out immunological diagnoses of malignant tumours. This method for producing an antiserum involves sampling an embryo at the foetal stage from animals of a same genetic type so as to obtain a cell suspension. After immunization, this method involves sampling spleen cells from the animal, separating lymphocytes and immunizing the animal of the same genetic line using the lymphocyte suspension. An antiserum is then obtained and cells originating from healthy organs of the same animals are added to the antiserum. The mixture is finally decanted and the liquid located above the sediments is filtered. In order to carry out a diagnosis, the filtrate is added to the subject's blood and the results are obtained by immuno-fluorescence, by blood tests or using other methods of immunological diagnosis. It is thus possible to diagnose a tumour when the reliable values obtained differ from reference values.

OCT-18-2000 12:10

COLLARD & ROE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT OR PATENTEE: VALENTIN SERGEEVICH ERKHOV

SERIAL OR PATENT NO.: PCT/RU98/00143

FILED OR ISSUED: MAY 18, 1998

GROUP:

TITLE: METHOD FOR PRODUCING A SPECIFIC ANTISERUM AGAINST THE
UNIVERSAL TUMOROUS ANTIGEN...

SMALL ENTITY DECLARATION

 FOR INDEPENDENT INVENTOR(S)

As a below-named inventor, I hereby declare that I am an independent inventor who (1) has not assigned, granted, conveyed, or licensed, and (2) is under no obligation under contract or law, to assign, grant, convey, or license, any rights in the invention, to any person who could not likewise be classified as an independent inventor if that person had made the invention, or to any concern which would not qualify as a small business concern or a nonprofit organization, as defined in 37 CFR 1.9(c).

 FOR SMALL BUSINESS CONCERN

I hereby declare that FREMISUR S.A. is a business concern which qualifies as a small business concern as defined in §1.9(d) - namely, (1) whose number of employees, including those of its affiliates, does not exceed 500 persons; and (2) which has not assigned, granted, conveyed, or licensed, and is under no obligation under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor if that person had made the invention, or to any concern which would not qualify as a small business concern or a nonprofit organization under this section; and that the exclusive rights to the invention have been conveyed to and remain with the above-identified small business concern.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like, so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the patent application or any patent issuing thereon.

Each of the undersigned hereby grants the firm of **COLLARD & ROE, P.C.**, 1077 Northern Boulevard, Roslyn, New York 11576, U.S.A., the power to insert in this Small Entity Declaration any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for filing and acceptance of this Declaration.

SMALL BUSINESS CONCERN:

By Alejandro Berlin Genis

Name: ALEJANDRO BERLIN GENIS
Title: DR. DIRECTOR OF FREMISUR S.A.

Date: MONTEVideo, OCTOBER 18, 2000

**METHOD FOR PRODUCING A SPECIFIC ANTISERUM AGAINST THE
UNIVERSAL TUMOROUS ANTIGEN AND METHOD FOR DIAGNOSING
MALIGNANT TUMOURS USING SAID ANTISERUM.**

FIELD OF INVENTION

The present invention pertains to the field of medicine, particularly to oncology, its spheres and diagnosing malignant tumors.

BACKGROUND OF INVENTION

A brief review of immunodiagnosis in the oncology shows the following.

In 1949 it was first mentioned by L.A. Zilber and in 1957 it was proved by T. Pran and G. Main that malignant cells have their own antigens.

According to Abilev there are 4 groups of antigens.

- 1) Viral tumorous antigens. They are identical for any viral tumor of this type.
- 2) Carcinogenic tumorous antigens. They are individual for patients as well as for tumors.
- 3) Isoantigens of transplantation type or tumorous-specific transplantation antigens. They are different in all individual types of tumors, induced by chemical agents. And they are the same in different tumors caused by the same virus.
- 4) Embryonic antigens.

During the process of carcinogenesis, cells are put to dedifferentiation, thus they acquire an embrional structure. In them there are to be found embryonic antigens, specific to embryonic development of organisms. These antigens can immunize the organism against tumors. The more studied antigens are the following: α – fetoprotein and cancer embryonic antigen (CEA). The former is to be found by carcinoma of the liver, the latter – by adenocarcinoma of the intestine, stomach, esophagus and pancreas.

Children having neuroblastoma, lymphosarcoma or tumor of the brain have α_2 – fetoprotein. Those who have carcinoma of the stomach have – fetal sulfoglycoprotein.

The above mentioned antigens are localized inside the cell membrane or circulate in the blood.

There is a specific group of antigens, so called heterospecific antigens, existing. They could not be classified as heterologous to the organism, while besides tumors they exist in other normal tissues. Among heterospecific antigens there is a renal antigen, which exists as a norm in the kidney and in the tumor of liver – hepatoma.

Adenocarcinoma of kidney contains an antigen of lungs and liver.

The immunological diagnosis of malignant tumors based on indication in the subject's blood the above mentioned antigens, antibodies to them and on revealing sensitized to tumoral antigen lymphocytes.

Methods for diagnosing lymphosarcoma, neuroblastoma are based on revealing α -fetoprotein. (On revealing antibodies to CEA – see Method in the Patent RU, 2077725, G. 01 N 33/53).

On revealing heterogenous antigens see Patent RU N 2063768, 1991, A 61K 39/00, Patent RU N 2025734, MPK G 01 N 33/53, author's certificate USSR N 170922, author's certificate N 1589215.

In the author's certificate N 1805392 (G 01 N 33/53) the method for diagnosing cancer by lymphocyte antigens (H_{la-b} 35) is described.

In fact, no test of the existing level of diagnosis is universal. Revealing antibodies in blood is a less reliable test, for in human blood there is a very wide spectrum of antitumoral and tissue antibodies. There is no method existing for revealing specific universal tumors antigen.

In this field perspective is revealing sensitized lymphocytes which inhibit the growth of malignant cells. Though, they are active only against "their own" type of tumor.

Thus, the used methods for tumor immunological diagnosis do not satisfy in all respects the requirements of primary diagnosis of tumors, they are totally unsatisfactory in screening malignant neoplasms and groups of high risk. Therefore they may be used to a certain degree only in immunomonitoring healing of malignant tumors.

Failures in existing methods may be explained by the fact that the used antiseraums against malignant tumorous antigens do not satisfy their own characteristics.

REVEALATION OF THE INVENTION

The aim of the Invention is producing antiserum against universal tumorous antigen, independent of tumor and organ type.

The prototype of the claimed method for producing specific antiserum as well as the method for diagnosis using the said antiserum is the method described in Patent RU N2063768, 1991, IPC, A 61 K 39/00. This method involves sampling tumor tissues from dead men, its freezing, obtaining a cell suspension, cell dispersion and decantation, extraction of antigens from supernatant fluid, extract immunization of animals, sampling blood from the immunized animals, obtaining the product from it, filling the specific antiserum into the reaction with the subject's blood, on the result of which a tumor is being diagnosed.

The claimed method unlike the well-known one allows obtaining antiserum for idotype of the T – cellular receptor functioning in malignant tumors. That is to obtain antiidotypic antiembrionic serum. That allows diagnosis of all types of tumors independently of their genesis and situs.

To accomplish the method for producing specific antiserum it is necessary to carry out two-stage immunization. That involves sampling an embryo at the foetal stage from animals of the same genetic type, dispersing it, obtaining cell suspension. Then the animal of the same genetic line is immunized by the cell suspension. After immunization it is necessary to sample spleen cells from the animal, to separate lymphocytes from the cell suspension at density gradient of 1,065-1,079. Using the above-mentioned lymphocytes it is necessary to accomplish multiple immunization of syngenic intact animals and then obtain antiserum from them using the standard method. This antiserum should be filtered (approximate diameter of pores in filters is 20 mcm).

The obtained antiserum has given reaction of precipitation with different types of tumors sampled from different people and in different organs.

It allowed devising methods for diagnosing malignant tumors on the basis of the obtained antiserum.

The well-known analogous methods for diagnosing tumors possess not high enough sensibility. Even the more effective among them have the sensibility level of not more than 40-60%. Such a low level of well-known oncologic immunodiagnostic tests can be explained so that the oncomarkers, used in said reactions, do not in fact satisfy their own characteristics. They are organo-specific or oncofetal antigens, characteristic of individual organisms or systems of organs in a norm. It leads to the following; an expected universal immunological expression of the only tumorformation mechanism peculiarities is substituted by individual, characteristic of not tumoral conditions (inflammation, collagenosis).

Organo-specific antigens are well-known for being not binding for tumoral cell-transformation. That gives high percent of pseudopositive results by diagnosing malignant tumors.

The proposed method for revealing of the oncomarker strongly differs from the well-known ones by disclosing a universal highly specific antigenic marker of tumoral growth, preserving during the whole period of tumoral progression.

The method is based on the results of author's theoretical and experimental works establishing that in histologically different cells of malignant tumors there is a stable in tumoral progression process functioning, which recognizes superficial embryospecific antigens. The said mechanism is proved to be on the basis of tumor formation (immortalization and progress) phenomena.

To carry out the method for diagnosing tumors it is necessary to obtain the specific antiserum using the proposed method, to fill the antiserum against universal tumoral antigen into immunological reaction with the subject's tissues or physiologic fluid. After it the tumor is diagnosed by immuno-fluorescence or by blood tests. Tissues of tumor in immuno-fluorescence reaction or the subject's blood test can be used as tissues.

The tumor diagnosis is proved by statistically reliable differences of the reaction results between tentative and control tests.

By obtaining the blood test the following formula for calculating the differences between tentative and control tests should be used:

$$\alpha = \frac{(A - \frac{B_1 + B_2}{2})}{X}$$

where α – diagnostic coefficient, if there is a tumor $\alpha \geq 1,5$

A – definition of blood test in tentative test (the antiserum for tumor antigen is added to the subject's citrated blood)

B_1 and B_2 – definition of the blood test in control tests (the serum of the same animal, used for obtaining the antiserum, is added to the subject's citrated blood)

X – maxim definition of the blood test in the test

A or the average B_1 and B_2 that is

$$B_1 + B_2$$

$$\frac{2}{-----}$$

VARIANTS OF INVENTION ACCOMPLISHMENT

An example of accomplishing methods for diagnosing malignant tumors.

At the foetal stage an embryo is sampled from Wister line rats, of 300 – 500g. Weight. The embryo's tissues are dispersed in the medium 199 at the following correlation of volumes and tissue: medium 199 1:5. The obtained suspension is used for weekly immunization of the intact Wister line rats.

After a period of 1,5 month spleen cells are taken from the animals, dispersed and at the phyco-verografin gradient 1.065 – 1.079 lymphocytes are obtained.

From the said lymphocytes the suspension is obtained: medium 199 at the correlation 1;1, which is weekly put into other intact rats. After five immunizations the rats are killed, the blood is taken from them, "lightened", the antiserum is obtained from it, filtered. With the above mentioned antiserum the blood test was taken from the below mentioned groups of patients. To carry out the blood test the standard capillary with innerdiameter about 0,8mm is used. 800 mcl of whole fresh venous blood, taken during the analysis, not late then 20 seconds after the moment of taking, is added to 200 mcl of 5% - sodium citrate bufer solution. The analysis should be carried out within 60 minutes since mixing the blood and the preservative. The analysis must not be taken in the case of hemolysis or coagulation. The said blood should be shared into 3 parts, 70mcl each, the parts should be put into three separate test-tubes. One of the parts should be added with a tentative (with antibodies) serum, the two others should be added with a control (without antibodies) serum, 20 mcl each. The serums are to be filled directly into the blood with preservative, not on the walls. The capillaries should be of the same size. The mixtures are mixed and filled into the capillaries till the level mark 5/0. This way they are to be kept 60 minutes. 60 Minutes later the indices are to be read and calculated according to the above mentioned mathematic formula.

The antiserum, obtained by the said method using Wistar line rats, was used for diagnosing disease with certain patients.

In the blood test of a patient K., 1942 y.o.,

d-s: rectum carcinoma, the obtained results were the following:

$$A=25, B_1=28, B_2=28$$

According to the mathematic formula the coefficient α was calculated:

$$(25 - \frac{28 + 28}{2}) \quad x 28$$

$$\alpha = \dots = 1,7$$

$1,7 > 1,5$, that is diagnosis malignant tumor was proved.

In the blood test of a patient with fibroma of lobule of the auricle the results were the following:

$$A=10, B_1=12, B_2=12$$

According to the mathematic formula the α coefficient was calculated:

$$\alpha = \frac{12+12}{(10 - \frac{12+12}{2})} \times 12$$

$$\alpha = \frac{12+12}{50} = 0,48$$

$\alpha < 1,5$, that is diagnosis of benign tumor was proved.

Below there are the results of investigating a group of patients having malignant tumors.

Comedocarcinoma – 125 patients

Sensibility – 83,2%

Carcinoma of the lung – 247 patients

Sensibility – 98,1%

Carcinoma of the stomach – 156 patients

Sensibility – 85,2%

Carcinoma of the colon intestine – 23 patients

Sensibility – 82,5%

Carcinoma of the rectum intestine 27 patients

Sensibility – 92,5%

Struma maligna – 58% patients

Sensibility – 79,5%

Carcinoma of the kidney – 38 patients

Sensibility – 78,6%

Carcinoma of the body of the womb – 412 patients

Sensibility – 75,0%

Carcinoma of the neck of the womb – 41 patients

Sensibility – 81,8%

Control group

Almost healthy – 400 patients

Sensibility – 5,1%

Mastopathia cystica-fibrotic – 221 patients

Sensibility – 8,3%

Gastritis – 120 patients

Sensibility – 6,2 %

Gastric ulcer – 62 patients

Sensibility – 8,3%

Collagenosis – 40 patients,

Sensibility – 6,5%

Pneumonia – 40 patients,

Sensibility 7,2%

(acute and chronic)

Prostatitis – 18 patients,

Sensibility – 2,1%

Chronic colitis – 115 patients,

Sensibility – 4,2%

INDUSTRIAL APPLICABILITY

Conclusion: The proposed method possesses sensibility not less than 92,4%, it is a highly effective diagnosing test.

In the application specific antiserum against universal tumoral antigen is the main component of the diagnosing device, on sale in Russia and abroad under the trade mark Turtest^R

CLAIMS

1. The method for producing specific antiserum for a universal tumoral antigen, involving sampling tissues, obtaining cellular suspension, immunization of animals, sampling blood from the immunized animals, obtaining the claimed product from it, characterized by multiple immunization, at the first stage as tissues an embryo at foetal stage is sampled from animals of the same genetic type so as to obtain a cell suspension, after immunization sampling spleen cells from the animal is carried out and lymphocytes are separated from the suspension, the subsequent immunizations of the animals of the same genetic types are carried out using the lymphocyte suspension, an antiserum is then obtained from the animal and cells of intact organs of the same animals are added, the mixture is decanted and the liquid located above the sediments is filtered.
2. A method as claimed in Claim 1, characterized in that filtration being carried out through porous filters.
3. Method for diagnosing malignant tumors using a specific antiserum against an universal tumoral antigen, involving sampling tissues, obtaining cell suspensions, immunizing animals, obtaining antiserum, filling it into reaction with blood or other physiologic liquids of the subject, on the results of this reaction a tumor is diagnosed, characterized by that the multiple immunization is carried out, as tissues at the first stage an embryo at foetal stage is sampled from animals of a same genetic type so as to obtain a cell suspension, after immunization sampling spleen cells from the animal is carried out, lymphocytes are separated from the suspension, the subsequent immunizations of the animals of the same genetic type are carried out using the lymphocyte suspension, an antiserum is then obtained from the animal, added to tissues, blood or other physiologic liquids of the subject with the following reading if the results by immuno-fluorescence, blood tests or other well-known methods for immunodetection, a tumor is then diagnosed by indices different from the control indices.
4. A method as claimed in Claim 3 characterized in that results of the blood test are calculated by the formula:

$$\begin{array}{c}
 | & & & & | \\
 & B_1 + B_2 & & & \\
 & (A - \frac{B_1 + B_2}{2}) & & & x \quad X \\
 | & & & & \\
 \alpha = \frac{50}{-----} & & & & \\
 & 50 & & &
 \end{array}$$

where: α - diagnosing coefficient, if there is a tumor it makes $\geq 1,5$

A – index of the blood test in the tentative test (an antiserum against tumor antigen is added to the subject's blood)

B_1 and B_2 – index of the blood test in control tests (the serum of the same genetic type of animal, used for antiserum producing, is added to the subject's blood)

x - maximum index of the blood test in the analysis (or in the test

A or average B_1 and B_2 , that is $B_1 + B_2$

$$\frac{-----}{2} .$$

COMBINED DECLARATION FOR PCT AND NATIONAL STAGE
(Includes Reference to PCT International Applications)

ERKHOV

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claim of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application.

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)		

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration numbers):

(6) FEDERICK J. DORCHAK, Reg. No. 29,298

ELIZABETH COLLARD RICHTER, Reg. No. 35,103

ALLISON C. COLLARD, Registration No. 22,532;

WILLIAM C. COLLARD, Registration No. 38,411

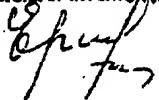
EDWARD R. FREEDMAN, Registration No. 26,048;

CHRISTOPHER B. GARVEY Registration No. 31,015

Send Correspondence to:		COLLARD & ROE, P.C. 1077 Northern Boulevard Roslyn, New York 11576		Direct Telephone Calls to (name and telephone number) (516) 365-9802
2	FULL NAME OF INVENTOR	FAMILY NAME ERKHOV (DECEASED)	FIRST GIVEN NAME VALENTIN	SECOND GIVEN NAME SERGEEVICH
0	RESIDENCE & CITIZENSHIP	CITY MOSCOW	STATE OR FOREIGN COUNTRY RUSSIAN FEDERATION	COUNTRY OF CITIZENSHIP RUSSIAN FEDERATION
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS Ul. Schepkina, 18-15	CITY 129090 MOSCOW	STATE & ZIP CODE/COUNTRY RUSSIAN FEDERATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR: 7/31



Galina Mikhailivna ERKHOVA

Wife and sole heir

address: ul. Malaya Krasnorskaya, d.10/3, kv. 11
107104 Moscow, Russian Federation

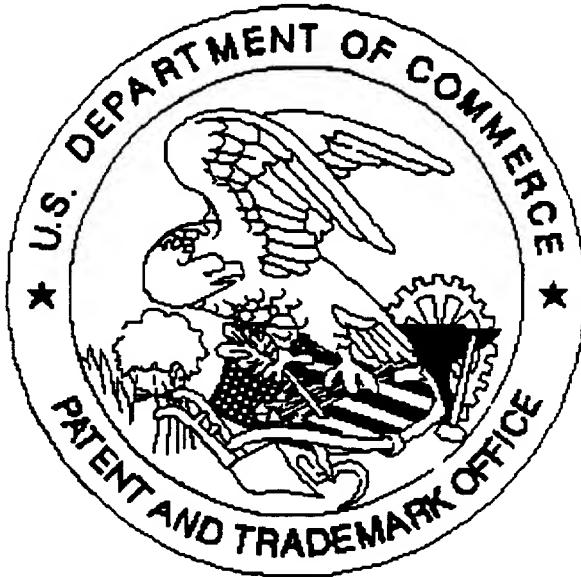


Country of citizenship: Russian Federation

DATE

26/12-2000

United States Patent & Trademark Office
Office of Initial Patent Examination -- Scanning Division



SCANNED # 26

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